AMENDMENTS TO THE CLAIMS

Please amend claims 1-8, 10, 11, 20, 21, 23, 24, 26, 28, 29, 31-39, 41, 42, and 45.

Please cancel claims 12-19 and 40.

Please add claim 60.

The listing of claims will replace all prior versions, and listings of claims in the application.

Listing of Claims

1. (Currently Amended) A method for detecting ~~and/or for detecting and distinguishing between or among~~ a colon cell proliferative disorder[[s]] in a human subject comprising:

a) ~~contacting genomic DNA isolated from~~ obtaining from the subject a biological sample comprising genomic DNA from blood plasma, blood serum, whole blood, or isolated blood cells[[,]]; or ~~cells isolated from the blood obtained from a subject~~

b) contacting the genomic DNA with at least one reagent~~, or series of reagents~~ that distinguishes between methylated and non-methylated CpG dinucleotide[s] sequences within ALX4 gene sequence (SEQ ID NO:5) ~~at least one target region of the genomic DNA, wherein said contiguous nucleotides comprise at least one CpG dinucleotide sequence~~; and

~~b) detecting, or detecting and distinguishing between or among colon cell proliferative disorders, wherein the detecting, or detecting and distinguishing is with~~ c) comparing the CpG methylation status in the sample with the CpG methylation status from a subject not having a colon cell proliferative disorder, wherein a difference in the CpG methylation status is indicative of a colon cell proliferative disorder ~~a sensitivity of greater than or equal to 80% and a specificity of greater than or equal to 80%~~.

2. (Currently Amended) The method of claim 1, wherein the CpG dinucleotide sequence ~~target region~~ comprises~~, or hybridizes under stringent conditions to~~ at least 16 contiguous nucleotides of the ALX 4 (SEQ ID NO:5) gene sequence.

3. (Currently Amended) A method for detecting~~, or for detecting and distinguishing between or among~~ a colon cell proliferative disorder[[s]] in a human subject[[,]] comprising:

determining~~, in a biological sample isolated from a subject,~~ the expression levels of ~~the~~ ALX 4 gene (SEQ ID NO:5) or gene sequences thereof, in a sample from the subject comprising colon cells, colon fluid, stool, or colon tissue; and

comparing the ALX 4 gene (SEQ ID NO:5) expression level in the sample with the expression level from a subject not having a colon cell proliferative disorder, wherein reduced expression of the ALX 4 gene (SEQ ID NO:5) in the sample as compared with the sample from the subject not having a colon cell proliferative disorder is indicative of a colon cell proliferative disorder.

4. (Currently Amended) The method of claim 3, wherein ~~said~~ the expression level is determined by detecting the presence, absence or level of mRNA transcribed from ~~said~~ the ALX 4 gene (SEQ ID NO:5) ~~or sequence~~.

5. (Currently Amended) The method of claim 3, wherein ~~said~~ the expression level is determined by detecting the presence, absence or level of a polypeptide encoded by ~~said~~ the ALX 4 gene (SEQ ID NO:5) ~~or sequence~~.

6. (Currently Amended) The method of claim 5, wherein ~~said~~ the polypeptide is detected by a method ~~one or more means~~ selected from the group consisting of immunoassay, ELISA immunoassay, radioimmunoassay and antibody binding.

7. (Currently Amended) The method of claim 3, wherein ~~said~~ the expression level is determined by detecting the presence or absence of CpG methylation within ~~said~~ the gene or

gene sequence thereof~~, wherein hypermethylation indicates the presence of a colon cell proliferative disorder~~.

8. (Currently Amended) A method for detecting~~, or for detecting and distinguishing between or among~~ a colon cell proliferative disorder[[s]] in a human subject[[,]] comprising:

a) obtaining, from the subject, a biological sample comprising genomic DNA from blood plasma, blood serum, whole blood, isolated blood cells, colon cells, colon fluid, stool, or colon tissue;

b) contacting the genomic DNA, or a fragment thereof ~~isolated from a biological sample obtained from a subject~~ with at least one reagent~~, or series of reagents~~ that distinguishes between methylated and non-methylated CpG dinucleotide[[s]] sequences within at least one target region ~~of the genomic DNA,~~ wherein the at least one target region comprises, or hybridizes under stringent conditions to [[a]] 9 contiguous nucleotides ~~sequence of at least 16 contiguous nucleotides~~ of ~~the~~ ALX 4 gene sequence (SEQ ID NO: 5), ~~wherein said~~ and the contiguous nucleotides comprise at least one CpG dinucleotide sequence; and~~, and whereby detecting, or detecting and distinguishing between or among colon cell proliferative disorders is afforded~~

c) comparing the CpG methylation status in the sample with the CpG methylation from a subject not having a colon cell proliferative disorder, wherein a difference in the CpG methylation status is indicative of a colon cell proliferative disorder.

9. (Canceled)

10. (Currently Amended) The method of claim 8, wherein the colon cell proliferative disorder is colorectal carcinoma ~~is distinguished from at least one condition selected from the group consisting of colon adenoma, normal colon tissue, non-colon tissues and non-colon cell proliferative disorders~~.

11. (Currently Amended) The method of claim 8, wherein the colon cell proliferative disorder is colon adenoma ~~is distinguished from at least one condition selected from the group consisting of colon carcinoma, normal colon tissue, non-colon tissues and non-colon cell proliferative disorders~~.

12-19. (Canceled)

20. (Currently Amended) A method for detecting~~, or for detecting and distinguishing between or among~~ a colon cell proliferative disorder[[s]] in a human subject ~~and healthy tissues in a subject,~~ comprising:

a) obtaining, from the subject, a biological sample comprising genomic DNA from blood plasma, blood serum, whole blood, isolated blood cells, colon cells, colon fluid, stool, or colon tissue;

b) contacting the genomic DNA, or a fragment thereof, ~~isolated from a biological sample obtained from a subject~~ with at least one reagent~~, or series of reagents~~ that distinguishes between methylated and non-methylated CpG dinucleotide[[s]] sequences; and

c) ~~within~~ amplifying at least one target sequence of the DNA with at least one primer pair, wherein the target sequence ~~at least one target region of the genomic DNA, wherein the at least one target region~~ comprises, or hybridizes under stringent conditions to [[a]] an at least 16 contiguous nucleotide sequence ~~of at least 16 contiguous nucleotides~~ of ~~at least two~~ a sequence[[s]] selected from the group consisting of SEQ ID NOS:5, 312, 313, 428, and 429 and a complement[[s]] thereof, wherein ~~said~~ the contiguous nucleotide[[s]] sequence comprises at least one CpG dinucleotide sequence.

21. (Currently Amended) The method of claim 8, comprising:

~~a) extracting or otherwise isolating genomic DNA from a biological sample obtained from a subject;~~

~~b)~~ a) treating the genomic DNA, or a fragment thereof, with one or more reagents to convert cytosine bases that are unmethylated in the 5-position thereof to uracil or to another base that is detectably dissimilar to cytosine in terms of hybridization properties;

~~c)~~ b) contacting the treated genomic DNA, or the treated fragment thereof, with an amplification enzyme and at least two primers comprising, ~~in each case a contiguous sequence of at least 9 nucleotides~~ that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:312, 313, 428 and 429 ~~SEQ ID NOS:304 to SEQ ID NO:535 and SEQ ID NOS:65 to SEQ ID NO:88~~, and complements thereof, wherein the treated genomic DNA or the fragment thereof is either amplified to produce at least one amplificate, or is not amplified; ~~and~~

~~d)~~ c) determining, based on a presence or absence of, or on a property of said amplificate, the methylation state of at least one CpG dinucleotide of a sequence selected within ~~from the group consisting of~~ SEQ ID NO[[S]]:5, or an average, or a value reflecting an average methylation state of a plurality of CpG dinucleotides ~~of a sequence selected from the groups consisting of SEQ ID NOS:5, whereby at least one of detecting, or detecting and distinguishing between colon cell proliferative disorders is, at least in part, afforded~~; and

d) comparing the CpG methylation status in the sample with the CpG methylation status from a subject not having a colon cell proliferative disorder, wherein a difference in the CpG methylation status is indicative of a colon cell proliferative disorder.

22. (Previously presented) The method of claim 21, wherein treating the genomic DNA, or the fragment thereof, comprises use of at least one reagent selected from the group consisting of bisulfite, hydrogen sulfite, and disulfite.

23. (Currently Amended) The method of claim 21, wherein the contacting ~~or amplifying~~ in ~~c)~~ b) comprises use of at least one method selected from the group consisting of[[:]] use of a heat resistant DNA polymerase as the amplification enzyme; use of a polymerase

lacking 5'-3' exonuclease activity; use of a polymerase chain reaction (PCR); and generation of an amplificate nucleic acid molecule carrying a detectable label.

24. (Currently Amended) The method of claim 23, wherein the detectable ~~amplificate~~ label is selected from the label group consisting of[[:]] fluorescent labels; radionuclides or radio labels; amplificate mass labels detectable in a mass spectrometer; detachable amplificate fragment mass labels detectable in a mass spectrometer; amplificate, and detachable amplificate fragment mass labels having a single-positive or single-negative net charge detectable in a mass spectrometer; and combinations thereof.

25. (Original) The method of claim 21, wherein the biological sample obtained from the subject is selected from the group consisting of cell lines, histological slides, biopsies, paraffin-embedded tissue, bodily fluids, stool, colonic effluent, urine, blood plasma, blood serum, whole blood, isolated blood cells, cells isolated from the blood and combinations thereof.

26. (Currently Amended) The method of claim 21, wherein the at least 9 contiguous nucleotides of b) ~~further comprising in step c) d) the use of at least one nucleic acid molecule or peptide nucleic acid molecule comprising in each case a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:312, 313, 428 and 429, and complements thereof, wherein said nucleic acid molecule or peptide nucleic acid molecule~~ suppresses amplification of the nucleic acid to which it is hybridized.

27. (Previously presented) The method of claim 26, wherein the sequence of said nucleic acid molecules is selected from the group consisting of SEQ ID NOS: 3030, 3035, 3046, 3058, 3062, 3067, 3070, 3074, 3077, 3079, 3082, 3087, 3095, 3099, 3102, 3106, 3112, 3120, 3125, 3129, 3132, 3141, 3143, 3154, 3156, and 3158.

28. (Currently Amended) The method of claim 26, wherein ~~said~~ the nucleic acid molecule or peptide nucleic acid molecule is ~~in each case~~ modified at the 5' [[-]]end thereof to preclude degradation by an enzyme having 5' -3' exonuclease activity.

29. (Currently Amended) The method of claim 26, wherein ~~said~~ the nucleic acid molecule or peptide nucleic acid molecule is ~~in each case~~ lacking a 3' hydroxyl group.

30. (Original) The method of claim 26, wherein the amplification enzyme is a polymerase lacking 5' -3' exonuclease activity.

31. (Currently Amended) The method of claim 21, wherein the determining in c) ~~d)~~ comprises hybridization of at least one nucleic acid molecule or peptide nucleic acid molecule ~~in each case~~ comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:312, 313, 428 and 429, and complements thereof, thereby producing hybridized nucleic acid molecules or peptide nucleic acid molecules.

32. (Currently Amended) The method of claim 31, wherein ~~said~~ the nucleic acid is selected ~~taken~~ from the group consisting of SEQ ID NOS:3030, 3035, 3046, 3058, 3062, 3067, 3070, 3074, 3077, 3079, 3082, 3087, 3095, 3099, 3102, 3106, 3112, 3120, 3125, 3129, 3132, 3141, 3143, 3154, 3156, and 3158.

33. (Currently Amended) The method of claim 31, wherein the at least one hybridized ~~such hybridizing~~ nucleic acid molecule or peptide nucleic acid molecule is bound to a solid phase.

34. (Currently Amended) The method of claim 31, wherein ~~a plurality of such~~ the ~~hybridizing~~ hybridized nucleic acid molecules or peptide nucleic acid molecules are bound to a solid phase in the form of a nucleic acid or peptide nucleic acid array selected from the array

group consisting of substantially linear ~~or substantially so~~, substantially hexagonal ~~or substantially so~~, substantially rectangular ~~or substantially so~~, and combinations thereof.

35. (Currently Amended) The method of claim 31, further comprising extending at least one ~~such~~ hybridized nucleic acid molecule by at least one nucleotide base.

36. (Currently Amended) The method of claim 21, wherein the determining in c) ~~d)~~, comprises sequencing of the amplificate.

37. (Currently Amended) The method of claim 21, wherein the primers of a) are ~~contacting or amplifying in c), comprises use of~~ methylation-specific primers.

38. (Previously presented) The method of claim 37, wherein the sequence of said methylation-specific primers is selected from the group consisting of SEQ ID NOS:3028, 3032, 3033, 3036, 3037, 3038, 3039, 3041, 3042, 3043, 3044, 3047, 3048, 3049, 3052, 3055, 3059, 3061, 3064, 3065, 3068, 3069, 3071, 3072, 3075, 3076, 3080, 3083, 3084, 3085, 3086, 3091, 3093, 3096, 3097, 3100, 3104, 3109, 3110, 3113, 3115, 3117, 3118, 3123, 3126, 3127, 3130, 3134, 3135, 3136, 3138, 3139, 3144, 3146, 3147, 3149, 3150, 3155, 3029, 3031, 3034, 3040, 3045, 3050, 3051, 3053, 3054, 3056, 3057, 3060, 3063, 3066, 3073, 3078, 3081, 3088, 3089, 3090, 3092, 3094, 3098, 3101, 3103, 3105, 3107, 3108, 3111, 3114, 3116, 3119, 3121, 3122, 3124, 3128, 3131, 3133, 3137, 3140, 3142, 3145, 3148, 3151, 3152, 3153, and 3157.

39. (Currently Amended) The method of claim 21, wherein the primers are ~~comprising in c) using primer~~ oligonucleotides comprising one or more CpG; TpG or CpA dinucleotides~~; and further comprising in d) the use of at least one method selected from the group consisting of: hybridizing in at least one nucleic acid molecule or peptide nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:312, 313, 428 and 429, and complements thereof; hybridizing at least one nucleic acid~~

~~molecule that is bound to a solid phase and comprises a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:312, 313, 428 and 429, and complements thereof; hybridizing at least one nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:312, 313, 428 and 429, and complements thereof, and extending at least one such hybridized nucleic acid molecule by at least one nucleotide base; and sequencing in d) of the amplificate~~.

40. (Canceled)

41. (Currently Amended) The method of claim 21, wherein the primers of b) are ~~comprising in c) amplification by primer~~ oligonucleotides comprising one or more CpG; TpG or CpA dinucleotides used for amplification and further comprising ~~in d)~~ hybridizing at least one detectably labeled nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:312, 313, 428 and 429.

42. (Currently Amended) The method of claim 21, comprising in ~~c)~~ b) the use of at least one nucleic acid molecule or peptide nucleic acid molecule comprising ~~in each case~~ a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:312, 313, 428 and 429, and complements thereof, wherein said nucleic acid molecule or peptide nucleic acid molecule suppresses amplification of the nucleic acid to which it is hybridized, and further comprising ~~in d)~~ hybridizing at least one detectably labeled nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:312, 313, 428 and 429, and complements thereof.

43. (Previously presented) The method of claim 39, wherein the primer oligonucleotides of c) are selected from the group consisting SEQ ID NOS: 3028, 3032, 3033, 3036, 3037, 3038, 3039, 3041, 3042, 3043, 3044, 3047, 3048, 3049, 3052, 3055, 3059, 3061, 3064, 3065, 3068, 3069, 3071, 3072, 3075, 3076, 3080, 3083, 3084, 3085, 3086, 3091, 3093, 3096, 3097, 3100, 3104, 3109, 3110, 3113, 3115, 3117, 3118, 3123, 3126, 3127, 3130, 3134, 3135, 3136, 3138, 3139, 3144, 3146, 3147, 3149, 3150, 3155, 3029, 3031, 3034, 3040, 3045, 3050, 3051, 3053, 3054, 3056, 3057, 3060, 3063, 3066, 3073, 3078, 3081, 3088, 3089, 3090, 3092, 3094, 3098, 3101, 3103, 3105, 3107, 3108, 3111, 3114, 3116, 3119, 3121, 3122, 3124, 3128, 3131, 3133, 3137, 3140, 3142, 3145, 3148, 3151, 3152, 3153, and 3157.

44. (Canceled)

45. (Currently Amended) A method for detecting~~, or for detecting and distinguishing between or among~~ colon cell proliferative disorders in a human subject[[,]] comprising:

a) obtaining, from [[a]] the subject, a biological sample comprising ~~having subject~~ genomic DNA from blood plasma, blood serum, whole blood, isolated blood cells, colon cells, colon fluid, stool, or colon tissue;

b) extracting, or otherwise isolating the genomic DNA;

c) contacting the genomic DNA of b), or a fragment thereof, comprising at least 16 contiguous nucleotides of ~~a sequence selected from the group consisting of~~ SEQ ID NO:5 and sequences that hybridize under stringent conditions thereto, with one or more methylation-sensitive restriction enzymes, wherein the genomic DNA is~~, with respect to each cleavage recognition motif thereof,~~ either cleaved thereby to produce cleavage fragments, or not cleaved thereby; ~~and~~

d) determining~~, based on a presence or absence of, or on property of at least one such cleavage fragment, the methylation state of at least one CpG dinucleotide of a sequence selected from the group consisting of~~ the CpG methylation status of SEQ ID NO:5, or an average, or a value reflecting an average methylation ~~state~~ status of a plurality of CpG dinucleotides of ~~a sequence selected from the group consisting of~~ target CpG dinucleotide sequences within SEQ

ID NO:5; and~~, whereby at least one of detecting, or of detecting and differentiating between or among colon cell proliferative disorders is, at least in part, afforded~~

e) comparing the CpG methylation status in the sample with the CpG methylation status from a subject not having a colon cell proliferative disorder, wherein a difference in the CpG methylation status is indicative of a colon cell proliferative disorder.

46. (Withdrawn) A treated nucleic acid derived from genomic SEQ ID NOS:5, wherein the treatment is suitable to convert at least one unmethylated cytosine base of the genomic DNA sequence to uracil or another base that is detectably dissimilar to cytosine in terms of hybridization.

47. (Withdrawn) A nucleic acid, comprising at least 16 contiguous nucleotides of a treated genomic DNA sequence selected from the group consisting of SEQ ID NOS:312, 313, 428 and 429, and sequences complementary thereto, wherein the treatment is suitable to convert at least one unmethylated cytosine base of the genomic DNA sequence to uracil or another base that is detectably dissimilar to cytosine in terms of hybridization.

48. (Withdrawn) The nucleic acid of claim 46, wherein the contiguous base sequence comprises at least one CpG, TpG or CpA dinucleotide sequence.

49. (Withdrawn) The nucleic acid of claim 46, wherein the treatment comprises use of a reagent selected from the group consisting of bisulfite, hydrogen sulfite, disulfite, and combinations thereof.

50. (Withdrawn) An oligomer, comprising a sequence of at least 9 contiguous nucleotides that is complementary to, or hybridizes under stringent conditions to a treated genomic DNA sequence selected from the group consisting of SEQ ID NOS:312, 313, 428 and 429.

51. (Withdrawn) The oligomer of Claim 49, comprising at least one CpG, CpA or TpG dinucleotide sequence.

52. (Canceled)

53. (Withdrawn) A kit useful for detecting, or for detecting and differentiating between or among colon cell proliferative disorders of a subject, comprising:

-a methylation-sensitive restriction enzyme; and

-at least one nucleic acid molecule or peptide nucleic acid molecule, comprising a contiguous sequence of at least 16 nucleotides that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:5, and complements thereof.

54. (Canceled)

55. (Withdrawn) A kit useful for detecting, or for detecting and differentiating between or among colon cell proliferative disorders of a subject, comprising:

-a bisulfite reagent; and

-at least one nucleic acid molecule or peptide nucleic acid molecule, comprising a contiguous sequence of at least 16 nucleotides that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:312, 312, 428 and 429, and complements thereof.

56. (Canceled)

57. (Withdrawn) The kit of claim 54, further comprising standard reagents for performing a methylation assay selected from the group consisting of MS-SNuPE, MSP, MethyLight, HeavyMethyl, COBRA, nucleic acid sequencing, and combinations thereof.

58. (Withdrawn) The kit of claim 52, wherein the length of the contiguous nucleotide sequence is selected from the group consisting of at least 17, at least 18, at least 20, at least 22, at least 23, at least 25, at least 27, at least 30, and at least 35 nucleotides.

59. (Withdrawn) The kit of claim 52, wherein the length of the contiguous nucleotide sequence is at least 18 nucleotides.

60. (New) The method of claim 1, wherein the detection of the colon cell proliferative disorder has a sensitivity of greater than or equal to 80% and a specificity of greater than or equal to 80%.